endometrioid (endo), mucinous (mucin), and serous (ser) type ovarian tumors as compared to normal ovarian epithelial (norm) samples (*Panel B*).

Please replace the paragraph beginning at page 7, line 21 with:

Figures 8A-D are graphs depicting the results of a quantitative PCR analysis of GPCR 4941 expression in human tumors (T) as compared to normal (N) tissue samples. *Panel* A, breast, ovary, and lung tumors; *Panel B*, colon and brain tumors.

REMARKS

Claims 1-69 were pending in the application. Claims 1-24 and 31-69 have been canceled without prejudice, as being drawn to a non-elected invention. Claim 26 has been amended and new claims 70-78 have been added. Accordingly, after the amendments presented herein have been entered, claims 25-30 and 70-78 will remain pending. For the Examiner's convenience all of the pending claims are set forth herein in Appendix A.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

Support for the new claims may be found throughout the specification and claims as originally filed. Specifically, support for claim 70 can be found, for example, at page 10, lines 10-29 of the specification. Support for claim 71 can be found at, for example, page 10, lines 31-34 of the specification. Support for claim 72 can be found, for example, page 10, lines 34-37 of the specification. Support for claim 73 can be found, for example, page 11, lines 1-7 of the specification. Support for claim 74 can be found, for example, page 13, lines 22-24 of the specification. Support for claim 75 can be found, for example, page 13, lines 25-30 of the specification. Support for claim 76 can be found, for example, page 14, lines 34-36 of the specification. Support for claim 77 can be found, for example, page 15, lines 1-7 of the specification. Finally, support for claim 78 can be found, for example, page 15, lines 25-28 of the specification.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite

the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objections

The Examiner has objected to the specification because the abstract exceeds 150 words in length. Applicants have edited the abstract so that it complies with MPEP §608.10(b).

The Examiner has further objected to the specification for the use of the abbreviation "MPM" in Figure 7 and for the fact that the Brief Description of the Drawings does not reflect that Figures 7 and 8 are multi-paneled.

Applicants respectfully submit that the abbreviation "MPM" stands for Millennium Predictive Medicine. This abbreviation followed by a number is simply the way the Applicants catalog samples. Further, Applicants have amended the Brief Description of the Drawings to reflect that Figures 7 and 8 are multi-paneled.

Lastly, the Examiner has objected to claim 26 because it "appears to be missing the word "is"." Applicants have amended claim 26 accordingly.

In view of the foregoing Applicants respectfully request that the Examiner reconsider and withdraw the objections to the specification and claims.

Rejection of Claims 25-30 Under 35 U.S.C. §101

The Examiner has rejected claims 25-30 under 35 U.S.C §101 because, according to the Examiner, "the claimed invention lacks a patentable utility." Specifically the Examiner is of the opinion that

> Applicants do little more than speculate that GPCR 4941 molecules "may be signal transduction proteins" (p. 9, lines 24-25). While Applicant demonstrates that the expression of GCPR 4941 is upregulated in a number of types of ovarian cancers, there is simply no demonstration of a causal relationship between GPCR 4941 gene expression or polypeptide activity and ovarian cancer or any of the very many other disorders taught in the specification. Given the lack of known function of the GPCR 4941 and the lack of causal relationship between it and any disease or disorder, there is no specific, credible utility for any compound that is found to modulation GPGR 4941 nucleic acid expression of GPCR 4941 polypeptide activity. Consequently, there is no specific, credible utility for a method of identifying such a compound.

Applicants' Specification Discloses A Specific, Substantial and Credible Utility for the Claimed Invention

Applicants respectfully traverse the forgoing rejection for the following reasons. The PTO Guidelines for Examination of Applications for Compliance with the Utility Requirement state that an invention has a well-established utility "(1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention, and (2) the utility is specific, substantial, and credible." (The Federal Register Vol. 66, No. 4, January 5, 2001, page 1098, column 1). Applicants respectfully submit that a *specific, substantial, and credible utility* is immediately apparent from Applicants' specification and the knowledge in the art at the time of Applicants' invention.

To begin with, Applicants' asserted utility is ***specific***. Applicants, using a variety of common techniques, show that GPCR 4941 gene expression was upregulated in 7 out of 8 ovarian serous tumor samples, 1 out of 4 endometriod tumors, 2 out of 2 mucinous tumors and 9 out of 9 serous type ovarian tumors (see Example 3). Applicants further show, in Example 1 that GPCR 4941 is upregulated in human endothelial cells exposed to laminar shear stress indicating that GPCR 4941 may be involved in the regulation of endothelial cell processes, *e.g.*, growth, proliferation, differentiation, migration and tube formation. In Example 2, Applicants show that GPCR 4941 is upregulated in the aortic arch region as compared to the abdominal aorta of apoE knockout animals, indicating a correlation with the pathogenesis of atherosclerosis. Accordingly, a compound that modulates the activity or expression of GPCR 4941 would have a specific utility of treating disorders associated with abnormal cell growth, *e.g* , ovarian cancer or cardiovascular disorders, *e.g.*, atherosclerosis.

Moreover, Applicant's asserted utility is ***substantial***. Since treating disorders associated with cancer and atherosclerosis is a desirable outcome based upon a need in the art, the disclosed use of the nucleic acid and protein molecules in the methods of the present invention is a substantial and a "real world" use (similar to a use of the protein for treating Alzheimer's disease, the example provided at pages 27-29 of the Utility Guidelines Training Materials).

In view of the teachings in Applicants' specification regarding overexpression of GPCR 4941 and the general knowledge in the art at the time of filing the application, the ordinarily skilled artisan would find Applicants' asserted specific and substantial utility to be ***credible***.

Based on the Utility Guidelines Applicants' Invention Has A Well-Established Utility

The hypothetical scenario in Example 12 of the *Revised Interim Utility Guidelines Training Materials* provides that a claim directed to a "receptor A" that is preferentially expressed in melanoma cells, but not in normal skin cells, has a well-established utility if it has been shown in the art that it is desirable to selectively detect melanoma cells as opposed to normal skin cells so as to diagnose that type of cancer. The well-established utilities of receptor A, as set forth in the *Utility Guidelines*, are a method of assaying for materials that bind to receptor A, or the making of a monoclonal antibody to receptor A for diagnosing melanoma. The rationale behind the foregoing conclusion, as presented by the *Utility Guidelines*, is that "[s]uch utilities are 'well-established' because the disclosure of the properties of the receptor and antibody taken together with the knowledge of one skilled in the art indicates that these specific, substantial and credible utilities were known."

Similarly, in the present case, the 4941 molecules of the present invention are "preferentially expressed" in tumor cells, such as ovarian tumor cells, and angiogenic tissues, and, thus, may be used to diagnose the types of tumors these molecules are preferentially expressed in, *e.g.*, ovarian tumors . The GPCR molecules may also be used to identify compounds which bind to or modulate GPCR, which compounds may, in turn, be used to treat, for example, cellular proliferation, growth, differentiation or migration disorders and disorders characterized by aberrant neo-vascularization. It is well known in the art that there exists a great need for diagnostics and treatments for these diseases.

As the Examiner is aware, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. §2164.07. Based on the evidence provided in the instant specification, *e.g.*, the expression data disclosed in the instant specification and discussed above, Applicant has shown a nexus between the 4941 molecules of the instant invention and their role in cellular proliferation, growth, differentiation, or migration disorders including cancer and angiogenesis. Applicant need not prove the asserted utility of the instant invention beyond a reasonable doubt.

In view of the foregoing, it is evident that the claimed methods of identifying modulators of the claimed GPCR 4941 molecules have a specific, substantial, and credible utility, which was

disclosed in Applicants' application as originally filed. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 25-30 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 25-30 under 35 U.S.C. §112, first paragraph as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention." The Examiner is of the opinion that

> [t]he specification describes a very broad range of cardiovascular disorders and tumorigenic disorders (see pp. 10-11) that may be treated by the compounds identified by the claimed method. As discussed above, there is no disclosure of the biological function of GPCR 4941 nor is there any disclosure of aberrant gene expression of GPCR 4941 or GPCR 4941 polypeptide activity being causal in any of these disorders. While the examples indicate that GPCR 4941 expression is upregulated in several types of ovarian tumors, some breast tumors, lung tumors and glioblastomas and may correlate with pathogenesis of artheriosclerosis (see Ex. 2 and 3), such correlations do not indicate a causal relationship between the upregulation of GPCR 4941 and the disorder. Therefore, it is entirely unknown if a compound which modulates with the nucleic acid expression or the polypeptide activity could possibly have any therapeutic value in any of the taught disorders. Furthermore, since the polypeptide activity of GPCR 4941 is unknown, the specification cannot possibly teach how to determine if a compound modulates the activity of PCR 4941.

Applicants respectfully traverse the foregoing rejection because, as indicated above, the claimed invention has a specific, substantial, and credible utility and, thus, one of skill in the art would know how to use the claimed invention. As indicated above, GPCR 4941 is overexpressed in cancerous tissue as well as in tissue of subjects suffering from cardiovascular disease. As a result, compounds which have the ability to modulate the expression or activity of GPCR are valuable in the treatment of cardiovascular and tumorigenic disorders. Applicants' specification discloses *ample* guidance as to how one of skill in the art would use the claimed invention to identify compounds capable of binding and/or modulating the activity of GPCR 4941. For example, Applicants disclose, at page 12, line 1 through page 20, line 14 methods of screening compounds for the ability to modulate GPCR 4941 activity. Applicants teach a myriad of cell-based and cell-free assays that can be used in the methods of the instant invention to identify modulators of GPCR 4941. For Example, Applicants teach at page 13, lines 21 through 30 that a compound's ability to modulate GPCR 4941 can be tested in a cell based assay by monitoring, for example, intracellular

calcium, IP_3, cAMP, or diacylglycerol concentration, the phosphorylation profile of intracellular proteins, cell proliferation and/or migration, gene expression of, for example, cell surface adhesion molecules or genes associated with angiogenesis or tumorigenesis, or the activity of a GPCR 4941-regulated transcription factor. Applicants further teach at page 14, lines 1-26 methods of detecting a compound's ability to interact with a GPCR receptor by using labeled or unlabeled substrates or ligands. Applicants also teach cell-free methods of identifying compounds that have the ability to modulate GPCR 4941 activity. For example, Applicants teach at page 15, lines 9-25 the use of cell-free assays to identify compounds capable of modulating GPCR 4941 using GPCR 4941 proteins, or fragments. As evident by the foregoing examples of methods disclosed in Applicants' specification, Applicants have provided ample guidance as to how a skilled artisan would identify compounds that have the ability to bind and/or modulate the polypeptides or nucleic acids of the instant invention. In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing section 112, first paragraph rejection of the pending claims.

Rejection of Claims 25-30 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 25-30 under 35 U.S.C. §112, second paragraph as being indefinite in reciting "GPCR 4941." The Examiner believes that, "[t]he specification suggests that this is both a family of G-protein coupled receptors (p. 8, lines 32-37) and yet also indicates that "GPCR4941" has a specific nucleotide sequence and amino acid sequence (p. 7, lines 34-37)."

Applicants respectfully traverse the foregoing rejection on the grounds that the term "GPCR 4941" is clear and definite in view of the teachings in Applicants' specification. Specifically, at page 8, lines 32-37 of the specification Applicants teach that " [t]he present invention is based, at least in part, on the discovery that G protein-coupled receptor (GPCR) genes, referred to herein as "G protein-coupled receptor 4941" or "GPCR 4941" nucleic acid and protein molecules." Applicants define a family of GPCR 4941 molecules in the instant specification that include, for example, allelic variants, homologues, and orthologues of the human GPCR 4941 shown in Figure 1 of the specification. The specific sequence referred to at page 7, lines 34-37 is the ***human*** GPCR 4941and represents only one member of the defined family.

Based on the foregoing teachings in Applicants' specification, one of ordinary skill in the art would find the term "GPCR 4941" to be clear and definite. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

The Examiner has also rejected claim 25 under 35 U.S.C. §112, second paragraph as being, "incomplete for omitting essential steps." Specifically the Examiner believes that "[t]he omitted step is: a step in which compounds identified by the recited method steps as modulating GPCR 4941 nucleic acid expression of GPCR 4941 polypeptide activity are determined to be capable of treating a cardiovascular or tumorigenic disorder."

Applicants traverse the rejection for the following reasons. Claim 25 is directed to

> [a] method for identifying a compound capable of treating a cardiovascular or tumorigenic disorder characterized by aberrant GPCR 4941 nucleic acid expression or GPCR 4941 polypeptide activity comprising ***assaying the ability of the compound to modulate GPCR 4941 nucleic acid expression or GPCR 4941 polypeptide activity, thereby identifying a compound capable of treating a cardiovascular or tumorigenic disorder*** characterized by aberrant GPCR 4941 nucleic acid expression or GPCR 4941 polypeptide activity.

Applicants respectfully submit that the claim, as filed, is not omitting an essential step. Since the GPCR 4941 nucleic acid and protein molecules used in the methods of the instant invention have been shown to be over expressed in cardiovascular and tumorigenic disorders, compounds that modulate the expression or activity of the GPCR 4941 molecules will be useful as therapeutic agents for disorders characterized by GPCR 4941 overexpression. Thus, "assaying the ability of the compound to modulate GPCR 4941 nucleic acid expression or GPCR 4941 polypeptide activity" is sufficient to identify a compound capable of treating a cardiovascular or tumorigenic disorder.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

In view of the foregoing amendments and foregoing remarks, it is respectfully submitted that the application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

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Limited Recognition Under 37 C.F.R. § 10(b)
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Date: November 14, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

26. The method of claim 25, wherein the disorder is a disorder associated with aberrant angiogenesis.

In the specification:

Figures 1*A-F* depicts the cDNA sequence and predicted amino acid sequence of human GPCR 4941 (GPR39; GenBank Accession AF034633). The nucleotide sequence corresponds to nucleic acids 1 to 2528 of SEQ ID NO:3. The amino acid sequence corresponds to amino acids 1 to 453 of SEQ ID NO: 2. The coding region without the 5' and 3' untranslated region of the human GPCR 4941 gene is shown in SEQ ID NO:1.

Figures 7*A-B* ~~is a~~ are graphs depicting the results of a quantitative PCR analysis of GPCR 4941 expression in ovarian tumors (T) as compared to normal (N) ovary samples (*Panel A*); and in endometrioid (endo), mucinous (mucin), and serous (ser) type ovarian tumors as compared to normal ovarian epithelial (norm) samples (*Panel B*).

Figures 8*A-D* ~~is a~~ are graphs depicting the results of a quantitative PCR analysis of GPCR 4941 expression in human tumors (T) as compared to normal (N) tissue samples. *Panel* A, breast, ovary, and lung tumors; *Panel B*, colon and brain tumors.

At page 92, line 7,

The present invention relates to methods and compositions for the diagnosis and treatment of cardiovascular disease, including, but not limited to, atherosclerosis, reperfusion injury, hypertension, restenosis, arterial inflammation, and endothelial cell disorders, such as disorders associated with aberrant endothelial cell growth, angiogenesis and/or vascularization, *e.g.*, tumorigenic disorders. Specifically, the present invention identifies GPCR 4941 genes which are differentially expressed in cardiovascular disease states, relative to their expression in normal, or non-cardiovascular disease states, and/or in response to manipulations relevant to cardiovascular disease. The present invention also identifies GPCR 4941 genes as differentially expressed in tumorigenic disease, *e.g.*, ovarian cancer. The present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular and tumorigenic diseases, and for the identification of subjects exhibiting a predisposition to such conditions. ~~The present invention~~

~~provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease and tumorigenic, and for monitoring the efficacy of compounds in clinical trials. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular and tumorigenic disease.~~

Appendix A

25. A method for identifying a compound capable of treating a cardiovascular or tumorigenic disorder characterized by aberrant GPCR 4941 nucleic acid expression or GPCR 4941 polypeptide activity comprising assaying the ability of the compound to modulate GPCR 4941 nucleic acid expression or GPCR 4941 polypeptide activity, thereby identifying a compound capable of treating a cardiovascular or tumorigenic disorder characterized by aberrant GPCR 4941 nucleic acid expression or GPCR 4941 polypeptide activity.

26. The method of claim 25, wherein the disorder is a disorder associated with aberrant angiogenesis.

27. The method of claim 25, wherein the disorder is a disorder associated with aberrant vascularization.

28. The method of claim 25, wherein the disorder is atherosclerosis.

29. The method of claim 25, wherein the disorder is ovarian cancer.

30. The method of claim 25, wherein the ability of the compound to modulate the activity of the GPCR 4941 polypeptide is determined by detecting the induction of an intracellular second messenger.

70. The method of claim 25, wherein the cardiovascular disorder is selected from the group consisting of ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, angina, heart failure, hypertension, myocardial infarction, coronary artery disease, aneurysm, cavernous angioma, tricuspid atresia, and truncus arteriosus.

71. The method of claim 25, wherein the cardiovascular disorder is an endothelial cell disorder.

72. The method of claim 71, wherein the endothelial cell disorder is selected from the group consisting of tumorigenesis, tumor metastasis, psoriasis, diabetic retinopathy, endometriosis, Grave's disease, ischemic disease, and chronic inflammatory diseases.

73. The method of claim 73, wherein the tumorigenic disease is selected from the group consisting of carcinoma, sarcoma, lymphoma and leukemia.

74. The method of claim 25, wherein the ability of the compound to modulate the activity of the GPCR 4941 polypeptide is determined by using a cell-based assay.

75. The method of claim 74, wherein the cell-based assay monitors intracellular calcium, cyclic AMP or diacylglycerol levels.

76. The method of claim 25, wherein the ability of the compound to modulate the activity of the GPCR 4941 polypeptide is determined by direct binding of a compound to GPCR 4941.

77. The method of claim 25, wherein the ability of the compound to modulate the activity of the GPCR 4941 polypeptide is determined by detecting the induction of a reporter gene.

78. The method of claim 25, wherein the ability of the compound to modulate the activity of the GPCR 4941 polypeptide is determined using a cell-free assay.